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REMARKS

Status of the Application

Applicants acknowledge with appreciation the withdrawal by the Examiner of the requirement of biological deposit under 35 U.S.C. 112, first paragraph, the rejection of claim 13 under 35 U.S.C. § 112, second paragraph, and all rejections under 35 U.S.C. § 102.

Claims 1-17 are now pending and stand rejected in the application. The following remarks address issues raised in the Office Action.

Issues relating to formalities of the specification.

The Examiner says that formal drawings previously submitted fail to comply with 37 CFR 1.84. Applicants will comply with the requirements upon a notice of allowable subject matter.

The specification has been amended as suggested by the Examiner to recite Figures 3A, 3B, and 3C in the Brief Description of the Drawings section.

Rejection of claims 3, 20-23 under 35 U.S.C. 112, first paragraph

Claims 1-8, 11, and 14-17 have been rejected for the alleged lack of enablement. There are several issues raised in the Office Action in maintaining the instant rejection. The following addresses these issues in turn.

1. Correlation between claim scope and enabling disclosure

The Examiner acknowledges enablement with respect to antibodies directed to the α4 subunit of VLA-4 and peptides having the formula set forth in SEQ ID NOs: 3-5. However, the Examiner maintains that the specification is not enabling with respect to other agents which inhibit binding of leukocytes to brain endothelial cells through leukocyte surface antigen alpha-4 integrin. The Examiner further asserts that "agents that inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "agent that specifically bind the alpha-4 subunit of VLA-4" include structurally unrelated compounds that would be expected to have greater differences in their activities, and that "there is insufficient direction or objective evidence as to how to make and to how to use" such agents, and as to whether an

effect encompassed by the claims can be achieved or predicted. As such, the Examiner concludes that there is a lack of correlation between the scope of the claims and the disclosure of the subject invention, and that undue experimentation would be required.

Enablement under §112, first paragraph, requires "that the specification teach those in the art to make and use the invention without undue experimentation." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). The Wands court held that a requirement for some experimentation, such as routine screening of monoclonal hybridomas to determine which ones secret antibody with the desired characteristics, does not indicate a lack enablement. Enablement simply requires that the necessary experimentation not be undue. In re Wands, 858 F.2d at 736-737. See also MPEP 2164.06(b). Thus, the test of enablement of the presently claimed invention is whether the agents recited in the claims can be routinely isolated following the teaching of the specification. The courts have noted that in production of variants of an exemplified species, even a considerable amount of individualized screening with its inevitable proportion of negative results is expected and considered routine by one of ordinary skill. In re Wands, 858 F.2d 731 (Fed. Cir. 1988). As discussed below, the procedures needed to produce other agents that can be used in the presently claimed methods are all routine, and no undue experimentation is required.

Applicants submit a declaration by Dr. Stephen Freedman. In the declaration, Dr. Freedman explains that the activity demanded of agents to inhibit leukocyte binding to brain endothelial cells via α4 integrin is a relatively simple one, that is, e.g., the capacity to bind to α4 integrin or VCAM-1 and thereby block binding of one of these molecules to the other (see paragraph 3 of the declaration). Dr. Freedman further explains that this type of activity can be screened in a high throughput assay that was routine in the art. With respect to anti-VCAM-1 agents, Dr. Freedman notes that there exist a repertoire of antibodies to VCAM-1 and methods for screening the antibodies. Dr. Freedman concludes that just as it would have been routine to screen antibody agents against α4 integrin, it would have also been routine to isolate antibody agents against VCAM-1 that can be used in the presently claimed invention (see paragraphs 4 and 5 of the declaration).

Turing to non-antibody reagents, Dr. Freedman explains that it is not necessary to have any knowledge in advance of a type of structure necessary to achieve such binding

(paragraph 8). Rather, what one needs is a significantly large pool of candidate molecules. As noted by Dr. Freedman in the declaration (paragraphs 6), and also described in the subject specification, such large pool of candidate molecules were available, e.g., as combinatory libraries, small organic molecules or natural products. Dr. Freedman explains that by screening sufficient candidate molecules, one expects to find some members with any desired binding specificity. Dr. Freedman illustrates this point by citing publications reporting nonantibody reagents that bind to VLA-4 and block its binding to VCAM-1 or vice versa. Dr. Freedman then concludes that it would have been a routine practice to isolate nonantibody agents to both VCAM-1 and α4 integrin with the requisite binding specificity (see paragraph 9 of the declaration).

It is submitted that Dr. Freedman's stature as an expert in the field merits appropriate deference. "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Guidelines for Examination of Applications for Compliance with the Utility Requirement at §B4. Appropriate deference by an Examiner to the opinion of an expert is also emphasized by In re Soni which holds that the opinion of an expert must be accepted "in the absence of evidence to the contrary." 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

In light of the above, Applicants submit that the subject specification enables the agents as recited in the presently claimed methods.

2. Incorporation by reference

With respect to references incorporated in the subject specification that disclose methods for screening reagents with the claimed binding characteristics, the Examiner says that these references are essential and therefore cannot be incorporated by reference. As such, the Examiner required Applicants to amend the specification to include the materials that have been incorporated by reference.

In response, Applicants point out that the presently claimed invention is not directed to specific agents that inhibit leukocyte binding to brain endothelial cells. Rather, the invention relates to use of such agents in treating viral encephalitis, and patentability of the

presently claimed methods does not reside on the agents per se. As such, Applicants submit that identity of the agent is not "essential materials" of the subject invention. As noted above, various reagents with the required binding characteristics are available. Other reagents can be identified by using various routinely practiced high throughput screening methods. However, all these reagents are exemplary rather than essential for the presently claimed methods.

In light of the above remarks, it is respectfully submitted that the claimed methods of treatment are enabled by the subject specification. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claims 1-17 under 35 U.S.C. 103(a) as allegedly "being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) and/or Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) and/or Soilu-Hanninen 1997 (J. Neuroimmunol. 72:95-105, 1997), in further view of the art known role or etiology of various viruses inducing encephalitis, as evidenced by Plant et al. (J. Virol. 69: 896-903, 1995) and/or the role of herpes viruses in multiple sclerosis, as taught by Sanders et al. (Archives of Neurology 53: 125-133, 1996) and/or Editorial (Archives of Neurology, 53: 123-124, 1996)." The Examiner says that "[w]hile it is noted that the claimed methods are distinguished from multiple sclerosis; it appears the combined teachings are consistent with the role of T cells in viral inflammation encompassing viral encephalitis and that there was sufficient motivation and reasonable expectation in inhibiting T cells via blocking VLA-4:VCAM-1 interaction to treat said viral inflammatory conditions wherein T cells contribute to the inflammation ...". Applicants respectfully traverse this rejection for the reasons stated below.

To establish a prima facie case of obviousness under 35 U.S.C. § 103, three basic criteria must be met. First, it must be shown that the prior art references when combined teach or suggest all of the claimed limitations. MPEP § 2142; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991); Litton Systems, Inc. v. Honeywell, 87 F.3d 1559, 39 U.S.P.Q.2d 1321 (Fed. Cir. 1996). Second, there must be some suggestion or motivation to combine reference teachings to produce the claimed invention. MPEP §§ 2142-2143 (7th Ed. 1998); In Re Dembiczak and Zinbarg, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). Third, it must be

shown that one of ordinary skill in the art would have had a reasonable expectation of success in practicing or carrying out the claimed invention. MPEP § 2142; In re Vaeck, 20 U.S.P.Q. 2d at 1442. As discussed below, the teachings of cited art do not meet these criteria.

The presently claimed methods are not obvious over the cited references in part because the cited art did not provide a reasonable expectation of success that use of agents against VLA-4 would be useful in treating viral encephalitis in human patients. The discussion in the prior art concerning use of such agents to block undesired inflammation in nonviral encephalitis is not applicable to treatment of viral encephalitis because in this disease, although the inflammation has undesired side effects, it also has a desired role in clearing the virus. The complex and unpredictable role of inflammation in viral infection is discussed at page 4, line 28 to page 5, line 5 of the specification. Because of a perceived desired and necessary role of inflammation in clearing viral infection, the skilled person would have expected that blockage of the response in viral encephalitis would be likely to be self-defeating. Blocking the response would have been expected to cause more viral activity, and thus induce more inflammation to combat it. In other words, suppression of the inflammatory response would be expected to undermine the patient's ability to fight the viral infection.

The above concerns regarding use of agents against VLA-4 to treat viral encephalitis illustrate a general principle that administration of immunosuppressants to virally infected patients is counterindicated. It is well known in the art that one of the major concerns in applying immune suppressive agents is the increased risk of infections by bacteria, viruses, fungal pathogens, and unusual opportunistic infections. See Goodman & Gilman's Pharmacological Basis of Therapeutics, Hardman et al. (Eds.), 9th edition, the McGraw-Hill Companies, 1996, page 1295 (copy attached). In addition, most if not all immune suppressive drugs currently prescribed by physicians have a warning label stating that immune suppression could increase susceptibility to infection. Examples of such immune suppressants currently on the market are shown in the attach pages taken from Physicians' Desk Reference (Medical Economics Company, 54th edition, 2000). These pages show that Neoral (with cyclosporine as the active ingredient), Cellcept, and SangCya, three of the few currently prescribed immune suppressive drugs, all have a warning stating that immunosuppression may increase the susceptibility to infection.

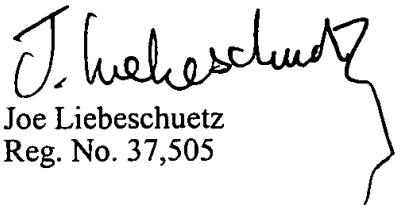
The references cited by the office action do nothing to alleviate the above concerns at using immunosuppressants to treat viral infection. It is acknowledged that Soilu-Hanninen 1997 discusses treatment of experimentally induced allergic encephalomyelitides (EAE) with VLA-4-specific mAb in mice infected with Semliki Forest Virus. However, the results obtained from EAE model are not applicable to viral encephalitis that occurs in humans. EAE is induced in mice by body irradiation and subsequent immunization with spinal cord homogenate. Although viral infection may increase the incidence of EAE in the treated mice (Soilu-Hanninen 1997, page 96, right column, 1st paragraph), the inflammatory response in these mice is directed not only to the virus, but also to the injected spinal cord homogenate. By contrast, in human viral encephalitis patients, the inflammation stems only from viral infection. Thus, the result of blocking VLA-4 in EAE mice could have been explained by its effect on inflammation due to injection of spinal cord and irradiation, and would not have predicted a similar response in a situation when the inflammation is solely directed against a virus.

Of the remaining cited references, Bendig discusses use of antibodies to VLA-4 in treating encephalitis, but not specifically viral encephalitis. As previously discussed, results from other kinds of encephalitis cannot be extrapolated to viral encephalitis due to the special role of inflammation in clearing the virus in this disease. Planz et al. report that CD8+ T cells apparently correlate with the development of neurological symptoms in viral encephalitis. However, this reference does nothing to suggest that blocking VLA-4 would not stimulate viral infection thereby increasing rather than diminishing the harmful CD8+ T cells.

For all of these reasons, Applicants submit that the cited art did not provide a reasonable expectation of success that treating human viral encephalitis by blocking inflammatory response with anti-VLA4 agents would be useful. Applicants respectfully request that the rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400 x 5209.

Respectfully submitted,



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Attachments:
1. Dr. Freedman's declaration, including Exhibits A-M;
2. Page 1295 of Goodman & Gilman's Pharmacological Basis of Therapeutics, Hardman et al. (Eds.), 9th edition, the McGraw-Hill Companies, 1996;
3. Pages from Physicians' Desk Reference (Medical Economics Company, 54th edition, 2000) regarding immune suppressive drugs.